

# Ethical Considerations in End-of-Life Care and Research

DAVID CASARETT, M.D., M.A.

## ABSTRACT

The goal of good palliative care is to relieve suffering and to improve quality of life. However, it is clear that access to palliative care is inconsistent. At least in part, these deficiencies exist because of a lack of solid evidence on which to base clinical decisions. Therefore, there is an urgent need for research that can define the standard of care and can increase access to quality care. This paper discusses six ethical aspects of end-of-life research that investigators and clinicians should consider in designing and conducting palliative care research. These include: (1) whether a study is research or quality improvement; (2) the study's potential benefits to future patients; (3) the study's potential benefits to subjects; (4) the study's risks to subjects; (5) subjects' decision-making capacity; and (6) the voluntariness of subjects' choices to participate in research.

## INTRODUCTION

THE GOAL OF GOOD palliative care is to relieve suffering and to improve quality of life. However, it is clear that access to palliative care is inconsistent. At least in part, these deficiencies exist because of a lack of solid evidence on which to base clinical decisions.<sup>1-3</sup> Therefore, there is an urgent need for research that can provide evidence to define the standard of care and to increase access to quality care.

Recent years have seen a dramatic increase in palliative care research, defined broadly as activities that are designed to contribute to generalizable knowledge<sup>4</sup> about end-of-life care. This growth has created a heterogeneous field that encompasses both qualitative and quantitative techniques, and descriptive as well as interventional study designs. The past 10 years have seen impressive growth in all of these areas.

However, despite the valuable knowledge that has been produced by this research, and the

promise of future important advances, its progress has been clouded by a persistent uncertainty about the ethics of these studies. Indeed, there have been concerns raised from several quarters about whether patients near the end of life should ever be asked to participate in any form of research.<sup>5,6</sup> Others have objected to this extreme position.<sup>2,7</sup> Nevertheless, many providers, institutional review boards (IRBs), ethics committees, study sections, and even investigators remain uncertain about the ethical limits of research involving dying patients. Because these concerns about the ethics of research create substantial barriers to advancing the field, they will be the focus of this article. Ethical issues of clinical care, while also significant, have been adequately addressed in other presentations and accompanying articles in this series.

Concerns about the ethics of end-of-life research have considerable intuitive appeal and must be taken seriously. Indeed, it would be unfortunate if the progress of palliative care re-

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Center for Health Equity Research and Promotion at the Philadelphia VA Medical Center, and the Division of Geriatrics, Institute on Aging, Leonard Davis Institute of Health Economics and the Center for Bioethics at the University of Pennsylvania, Philadelphia, Pennsylvania.

search were slowed by the sorts of ethical scandals that have threatened other fields of research that involve vulnerable populations, such as those with mental illness.<sup>8</sup> However, strict oversight and tight limits on palliative care research have the potential to do equal damage to a growing field. Therefore, to avoid potential scandals without imposing excessive regulation and oversight, it is important that palliative care investigators and clinicians consider these concerns in a fair and balanced way.<sup>9</sup>

This article discusses six ethical aspects of end-of-life research that investigators and clinicians should consider in designing and conducting palliative care research. These include: (1) whether a study is research or quality improvement; (2) the study's potential benefits to future patients; (3) the study's potential benefits to subjects; (4) the study's risks to subjects; (5) subjects' decision-making capacity; and (6) the voluntariness of subjects' choices to participate in research. In this discussion, the terms "palliative care research" and "end-of-life research" are used interchangeably to refer to the area of their overlap—the care of patients with serious life-limiting illness.

## DEFINING RESEARCH

The first—and arguably the most important—question that palliative care investigators face in designing an ethical study is whether it is research or quality improvement (QI). This decision is extremely important, and it has profound implications for the study's design and the ethical standards to which it will be held. For instance, federal law requires research projects to be reviewed by local institutional review boards (IRBs) to ensure that informed consent is obtained from each subject, that research risks are reasonable in relation to expected benefits, and that subjects are recruited in an equitable fashion.<sup>4</sup> In comparison, there are few widely accepted standards that govern QI.<sup>10</sup>

In many situations, it is clear that a planned study is research. For instance, there is likely to be general agreement that randomized clinical trials comparing one or more pain medications, or population-based studies of symptom prevalence are research, and should be held to the ethical standards for research. However, QI activities often share many of the attributes of research. For instance, both QI and research involve sys-

tematic data collection methods, such as surveys and chart reviews. Both may apply statistical methods to test hypotheses, establish relationships among variables, and to evaluate outcomes. Finally, both are designed to produce knowledge that could benefit patients other than those directly involved in the activity. In practical terms, therefore, QI and research activities can be difficult to distinguish. This can produce confusion and conflicting opinions from IRBs that review study protocols.<sup>11</sup>

These distinctions are likely to be particularly difficult in end-of-life research. Although there is an urgent need to advance the science of end-of-life care, there is an equally pressing need to ensure that the evidence that is available is actually applied to clinical care. Indeed, many of the widespread deficiencies in end-of-life care are arguably caused not by the lack of an evidence base, but rather by a lack of awareness of that evidence base and a failure to apply it to clinical practice. These sorts of aims—improving clinical practice and reducing unwanted variation—are ideally suited to methods of QI.

Unfortunately, the federal regulations that make the distinction between research and QI so important offer little practical assistance in distinguishing between the two types of activities. In those regulations, research is defined as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."<sup>4</sup> Although elegant in its simplicity, this definition may prove prohibitively difficult for palliative care investigators to apply. It is often not clear how systematic an activity needs to be in order to be considered research. Nor is it clear how generalizability should be defined, or how an investigator's intent should be measured.

In an effort to make the distinction between QI and research more clear, several additional criteria have been proposed. These include the degree to which a study deviates from standard care, whether an activity requires identifiable recruitment practices, how individuals are selected to receive a particular intervention, the degree of uncertainty associated with the intervention, and whether the patients involved benefit from the knowledge to be gained.<sup>10,12,13</sup> One of the most recent of these<sup>10</sup> describes a two-step algorithm that investigators may find useful when the existing criterion of an intent to produce generalizable knowledge<sup>4</sup> fails to provide adequate guid-

ance. This algorithm may prove to be too restrictive, as some have argued.<sup>14</sup> In any event, none of these guidelines should take precedence over existing federal regulations,<sup>4</sup> and they are at most heuristics that may be useful.

#### *Defining research: summary and recommendations*

Palliative care investigators face challenges of distinguishing between research and QI that are uniquely difficult, because the focus of end-of-life research is often on overcoming barriers to high quality care. To overcome these difficulties, funders should:

- Support research that can inform a consensus about the role that research and QI methods should play in defining and improving the standard of end-of-life care
- Encourage the use of QI methodologies in requests for applications (RFAs) for which they may be appropriate (e.g., overcoming barriers to symptom management);
- Encourage a consensus regarding appropriate levels of review for minimal risk studies that use QI methods.

### **BENEFITS TO FUTURE PATIENTS: A STUDY'S VALIDITY AND VALUE**

Implicit in the goal of end-of-life research is the expectation that studies will generate knowledge that will eventually improve care for future patients. Therefore, the second ethical aspect of end-of-life research that deserves consideration is its potential benefits for future patients. These benefits to others can be described in terms of validity and value. Although both validity and value are often categorized as scientific or methodological issues, they also have profound ethical implications.

#### *Validity*

End-of-life studies must use techniques of design and data analysis that peer reviewers can agree are appropriate. These requirements collectively describe a study's validity.<sup>15</sup> Validity is a threshold requirement for all research, because it is unethical to expose human subjects to risks in studies that peer reviewers agree cannot adequately answer a research question.<sup>16</sup> Therefore,

at a minimum, all investigators must routinely consider a study's validity.

Although the requirement of validity is universal in medical research, there are several reasons why it poses particularly difficult challenges in palliative care research. For instance, palliative care research is a relatively new field, and investigators have not yet arrived at a consensus about optimal measurement techniques. Even endpoints as simple as pain can be measured in a variety of different ways, using different scales and even composite measures.<sup>17</sup> The wide variety of measurement approaches in use makes evaluation of a study's validity difficult. Furthermore, these difficulties are exacerbated in attempts to measure more diffuse constructs such as spiritual well-being or quality of life.

#### *Value*

Above this threshold of validity, palliative care studies may offer more or less importance or "value." Broadly, value can be defined as the likelihood that a study's results will improve the health and well-being of future patients.<sup>18,19</sup> In addition, a study must be designed to produce knowledge that is generalizable. Indeed, generalizability is the cornerstone of the Common Rule's definition of research: "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."<sup>4</sup>

Like validity, value is an important measure of a study design's scientific quality, but it is also a measure of its ethical quality because a central goal of research is to produce knowledge that will ultimately be "important,"<sup>4,20</sup> "fruitful,"<sup>21</sup> or "valuable."<sup>22</sup> In fact, one reason that subjects participate in clinical research is to produce knowledge that will benefit others.<sup>23</sup> Because subjects are willing to accept risks and burdens of research at least in part to benefit others, investigators have accepted an ethical responsibility to maximize the probability that a study will be able to do so. Therefore, in addition to widely accepted scientific arguments for valuable research, there are compelling ethical arguments as well.

End-of-life researchers may also face unique challenges of ensuring a study's value. The challenges of research recruitment in this population (discussed below) mean that many palliative care studies have included small sample sizes and, often, homogeneous study populations drawn from

a single setting. The results of these studies, therefore, may offer limited generalizability. This is particularly true of studies conducted in academic medical centers, the findings of which may have limited applicability to patients who receive care at home. Finally, trials that fail to recruit adequate numbers of patients because of recruitment problems may produce results that are not sufficiently compelling to change clinical practice.

### *Maximizing validity and value in palliative care research*

Space does not permit a comprehensive overview of ways in which a palliative care study's validity and value can be assessed and improved. Indeed, such a discussion moves quickly beyond ethics and into the technical language of study design and health measurement. Nevertheless, several broad recommendations are possible.

First, a study's sample size should be adequate to answer the research question that is posed. Problems of underpowered studies, and particularly clinical trials, are both widespread and well described.<sup>24</sup> However, issues of power and sample size are particularly relevant to pain and symptom research, in which random variation can be quite large.<sup>25</sup> To minimize these problems, it may be useful to establish consortia or collaborative groups that can participate in multicenter studies. Such arrangements have been highly effective in promoting research on rare disorders, and may be applicable as well to palliative care research, in which investigators are limited and available patients are often sparse.

In addition, techniques to enhance recruitment through "research screening" questionnaires show promise in identifying potential subjects.<sup>26</sup> These screening questions can be used to identify patients who are interested in research and who are willing to be approached by an investigator. Although it is not known whether these techniques actually increase recruitment and decrease selective enrollment, they have been found to be feasible in a variety of settings and should be the focus of future research.<sup>26,27</sup>

Second, palliative care investigators can enhance the ethical quality of a study by taking reasonable steps to increase the generalizability of its results. These steps might include sample size calculations that permit subgroup analysis of groups of patients that have typically not been the focus of investigation, such as patients with

noncancer diagnoses, or patients who are elderly. The generalizability of a study's results might also be enhanced by recruiting subjects outside academic medical settings, because preliminary evidence suggests that these patients, and their needs for care, may be different than those who receive care in academic settings.<sup>28</sup>

In addition, palliative care investigators can enhance the generalizability, and therefore the value, of their research by making reasonable efforts to include patients who are receiving care at home, and particularly those who are enrolled in a home hospice program. Substantial barriers may make it difficult to include these patients in research. Nevertheless, few data are available to guide the management of home care patients near the end of life, and palliative care investigators can enhance the value of their research by including this population whenever possible.<sup>29</sup>

Finally, investigators can enhance a study's value by including measures and endpoints (for interventional trials) that are important to patients and their families. Unlike studies in many other fields, where endpoints such as death or hospitalization are the norm, palliative care investigators may also consider other endpoints. In a study of malignant bowel obstruction, for instance, one might also assess resumption of a regular diet, pain, nausea, time spent at home, or a variety of other measures. The choice of these measures, and the value of the study's results, depend upon careful incorporation of patients' and families' preferences and values.

Of course, all of these improvements in generalizability come at a substantial cost. For instance, studies that recruit subjects from several different settings require more elaborate designs for recruitment and follow-up. In addition, investigators who include plans for subgroup analysis in their sample size calculations face rapidly escalating sample size requirements and costs. However, steps like these offer an important way to enhance a palliative care study's value and therefore its ethical quality. Therefore it will also be important that funding agencies understand the ethical importance of generalizability, and that generalizability comes with a financial cost.

### *Validity and value: summary and recommendations*

End-of-life investigators face unique ethical challenges of maximizing the validity and value



of their studies, because of the state of the science and nature of the patient population. To ensure that end-of-life studies produce data that are both valid and valuable, funders should:

- Support research that can inform a consensus about standard measures of common constructs (e.g., pain, symptom burden, quality of life)
- Encourage and support studies that recruit from underrepresented populations (e.g., ethnic minorities, home hospice patients, nursing home residents)
- Encourage and support studies that are adequately powered to evaluate subgroup differences
- Support research that defines patient-centered endpoints, which reflect a patient's unique goals and preferences
- Support the evaluation of "research screening" techniques that identify patients and families who are interested in research participation.<sup>26,27</sup>

## BENEFITS TO SUBJECTS

Palliative care investigators can also enhance the ethical rigor of a study by maximizing the benefits that it will offer to subjects. Broadly, these benefits can be considered under two categories: (1) benefits to subjects during the study, and (2) benefits from the data that are collected. Each of these is discussed below.

### *Benefits to subjects during the study*

Investigators may have several opportunities to maximize potential benefits of research to the subjects who participate. Perhaps the first, at least in an interventional study, is in their choice of an intervention. Ideally, a new intervention to be studied should have a reasonable chance of success. More important, though, if it is to offer subjects a significant potential benefit, an intervention should offer the possibility of a meaningful improvement over other interventions that are available to subjects outside the study. For instance, a pain management algorithm that is expected to reduce cancer pain<sup>30</sup> would only offer potential benefits if it is qualitatively or quantitatively different than those that constitute the usual standard of care. On the other hand, a com-

parison of two medications that are commercially available, such as topical fentanyl and sustained release morphine would not *per se* offer subjects any potential benefit, although there may be indirect benefits from better pain assessment and management on protocol. This is true even if the study's results offer considerable clinical value.<sup>31</sup>

The potential benefits of a study can also be enhanced by choosing an active control design, rather than a placebo.<sup>31</sup> If a placebo is used, a study's potential benefits can be improved by altering the standard 1:1 randomization scheme in a placebo-controlled trial in a way that increases subjects' chances of receiving an active agent.<sup>32</sup> Finally, the potential benefits of a placebo-controlled trial can also be enhanced by using a crossover design, so that all subjects are offered potential benefits, if the medication's pharmacokinetic profile makes it possible to avoid carry-over effects.

These suggestions should be tempered by two caveats. First, the potential benefits of research are never certain. If they were, a randomized trial would not be ethically acceptable. That is, a legitimate argument for the uncertainty that justifies a clinical trial, or equipoise, could not be made.<sup>33</sup> However, investigators generally design studies of interventions for which there is at least some evidence of effectiveness. Therefore, even though these potential benefits are not certain, they are more or less likely, and this assessment of likelihood should be considered in the design of pain research.

Second, palliative care studies need not always offer potential benefits. Indeed, many, and perhaps most, will not. Nevertheless, when a study does offer potential benefits, investigators may consider enhancing a study's potential benefits in these ways. The importance of doing so is particularly great if other aspects of a study raise ethical concerns, which might be the case if subjects' decision-making capacity is limited, or if the study's risks are substantial.

### *Benefits from data collected during a study*

Although the opportunities to enhance potential benefits described above apply largely to studies involving palliative care interventions, another opportunity applies equally well, if not better, to research that is descriptive. A common ethical issue in the design of palliative care research, and particularly descriptive research, is

the possibility that data gathered may contribute to a subject's care. For instance, data gathered during a descriptive study may identify pain that is inadequately treated,<sup>34-36</sup> dissatisfaction with pain management,<sup>37-39</sup> or related clinical problems such as depression.<sup>36,40,41</sup>

In anticipation of instances like these, investigators can design standard operating procedures that help to ensure that valuable clinical information is made available to the subject and that individual's clinicians. At the least, these procedures should provide data about the presence of unrecognized and untreated symptoms, and concurrent disorders like depression. This is arguably an ethical obligation of all symptom-oriented research.<sup>7</sup>

#### *Benefits to subjects after a study has ended*

Investigators can also enhance the potential benefits for subjects after a study has ended. These sorts of post-study benefits are not usually included in assessments of a study's balance of risks and benefits. In a sense, they are components of a study's value, because these benefits generally come from the knowledge that the study produced. Nevertheless, subjects themselves may benefit from the knowledge to be gained from a study if the study's results are applied to their care. Investigators have numerous opportunities to ensure that these results are translated into improvements in subjects' post-study care and, by doing so, can enhance the study's potential benefits to subjects.

For instance, subjects in palliative care research can benefit after a study if they learn from the study's aggregate results. This might be the case if a study comparing two pain medications finds that one resulted in fewer side effects overall.<sup>31</sup> Subjects in the study would benefit from these data because this knowledge should allow them to make a more informed choice among available medications. Subjects might also benefit from results that are specific to them. For instance, if a subject receives two medications in a blinded crossover trial, and prefers one to the other, that individual would be better able to choose between these medications in future clinical situations, armed with the results of a blinded comparison of the two.<sup>42,43</sup>

Finally, investigators can increase the likelihood that subjects have continued access to medications that are studied. If medications are not

available, either due to high cost or because the medication has not yet received regulatory approval, subjects will not benefit (immediately) from the study's results. Thus by arranging reduced rate programs or open label extension phases, investigators can increase a study's potential benefits for subjects by helping to ensure that subjects will benefit from the study's results.<sup>44</sup>

This benefit may be particularly important in palliative care research, because mortality rates in some studies are very high. This means that subjects may not live long enough to see a study medication's approval for clinical use, or to see a study's results published and translated into improved care. For this reason, it is especially important that investigators consider mechanisms by which results can be applied to the care of research subjects in a timely fashion.

#### *Benefits to subjects: summary and recommendations*

End-of-life investigators may have a variety of opportunities to enhance the potential benefits to study subjects and, in the process, to enhance to ethical merits of a study. To support these efforts, funders should:

- Encourage and support investigators' efforts to provide study results to research subjects and their health care providers
- Encourage and support investigators' efforts to make successful interventions available to subjects after a trial has ended
- Encourage study protocols that prescribe responses to patients who are identified as having uncontrolled symptoms.

### **MINIMIZING RISKS AND BURDENS**

Investigators can also enhance a study's ethical soundness by taking steps to minimize a study's risks and burdens. Although the distinction between risks and burdens is not always clear, a rough heuristic is useful. In general, a risk can be considered as the probability of an adverse medical event or undesirable outcome. Risks might include side effects of a medication, or increased pain during a study. The term "burden" can be used to describe those unpleasant features of participation in a study that are more certain,

and which are better thought of as inconveniences. Additional clinic visits, time spent filling out questionnaires, or time spent waiting in clinic might be described as burdens.

### *Identifying risks and burdens*

Attention to the ethical design of palliative care research, and to the minimization of research risks and burdens, requires a clear agreement about how they should be defined. The criteria by which study risks and burdens are identified and evaluated uses the concept of incremental or “demarcated” risks imposed by participation in a study.<sup>45</sup> For instance, the application of this standard to interventional pain research would mean that investigators designing a trial to compare the effectiveness of two opioids need not go to great lengths to justify the risks of the opioids being evaluated, if subjects in the trial would have received similar medications, with similar risks, off protocol. Of course, the risks of any medication in a clinical trial should be disclosed in the informed consent process.<sup>4</sup> Nevertheless, investigators are not under the obligation to minimize or justify these risks as they would be if, for instance, the same medications were being given to patients with mild pain, who would not receive them as part of standard care.

*Minimizing risks: interventional trials.* Perhaps one of the most contentious and emotional questions in palliative care research,<sup>46,47</sup> and indeed in research generally,<sup>48-50</sup> is whether a placebo or sham control arm is ethically appropriate. The ongoing debates about the scientific merit of these controls, and the competing advantages of active control superiority trials and equivalency trials are beyond the scope of this discussion. However, several general points can be made about the ethics of placebo- and sham-controlled trials. Each of these designs is discussed below.

Broadly, placebos can be defined as interventions that are “ineffective or not specifically effective” for the symptom or disorder in question.<sup>51</sup> Increased attention to the ethical issue of placebo controls in recent years has produced a growing consensus that all subjects in a clinical trial should have access to the best available standard of care.<sup>52</sup> Thus in infectious disease research, for instance, all subjects with meningitis would have access to an antimicrobial agent that has proven effective. However, this requirement may

be difficult to apply to studies of treatment for pain, other symptoms, or depression, in which the placebo response can be quite substantial. These difficulties are compounded when the symptom being studied is transient, such as incident pain.<sup>32</sup>

For these reasons, it is not practical to prohibit placebos in palliative care research, and a placebo control may be ethically acceptable in several situations. First, placebos are acceptable if subjects receive a placebo in addition to the standard of care. For example, subjects might be randomly assigned to receive an opioid for pain, or an opioid plus an adjuvant agent. Second, a placebo arm is justified if the symptom under study has no effective treatment. For example, the transient nature of incident pain often defies adequate treatment on an as-needed basis, and a placebo control might be justified in a randomized controlled trial of a novel agent for the treatment of incident pain. Third, a placebo control is justified if subjects have adequate access to breakthrough or “rescue” treatment. This may in turn alter a trial’s endpoints. For instance, the free use of breakthrough dosing in a trial suggests the possible inclusion of these doses as a study endpoint, either directly<sup>53,54</sup> or as part of a composite endpoint.<sup>17,55</sup>

Concrete recommendations about sham procedures are somewhat more elusive, in part because sham procedures themselves are difficult to define. In general, though, sham procedures in palliative care research involve the use of a control procedure such as a nerve block, which is administered in a way that makes it ineffective.<sup>56</sup> These procedures create ethical concerns because some subjects, or all subjects, depending on the study’s design, are exposed to the risks of the procedure without hope of its benefits.<sup>48</sup> However, like placebo controls, shams also have a role in palliative care research, because the nonspecific therapeutic effects of surgery may be substantial. For instance, Leonard Cobb’s research in the 1950s effectively debunked a widely used cardiac procedure that, if it had been widely disseminated, would eventually have put thousands of patients at risk.

Palliative care investigators have an opportunity to reduce these concerns substantially in the design of a sham-controlled study. For instance, investigators might conduct these studies in a setting in which the procedure itself (whether sham or real) poses few if any additional, or “incre-

mental” risks above and beyond usual care. Investigators might insert a sham epidural catheter that would then be used for post-operative analgesia.<sup>57</sup> When this is not possible, investigators can choose a crossover design, in which subjects are assigned to receive either the sham or the real procedure, followed by the other. This design does not decrease the incremental risks of the sham procedure. However, it does ensure that all subjects who bear the risks of the sham procedure also have access to the real procedure’s potential benefits. This crossover sham design has been used in other settings,<sup>58</sup> and might be appropriate for pain research when the risks or discomforts of the sham procedure are substantial.

*Minimizing risks: descriptive studies.* The vast majority of descriptive studies present only minimal risks. However, some IRBs and funders have expressed concerns about end-of-life studies involving interviews with patients or families, and the risk of distress that they may cause. It is likely that these risks of distress are very small in most studies, and that they may be balanced by the benefits that subjects perceive (e.g., from the opportunity to talk about difficult issues).<sup>59-61</sup> Although most research to define the risk of distress has been qualitative,<sup>59,60</sup> limited quantitative data indicate that the risk of self-reported distress varies widely among studies and is related to subject characteristics.<sup>61</sup> Therefore, it is not appropriate to assume that all descriptive studies that involve sensitive interviews pose a significant risk of distress. However, it is prudent to use simple strategies to identify and address distress when it occurs (e.g., by providing access to a counselor).

*Minimizing burdens.* For the most part, opportunities to minimize burdens are readily apparent. For instance, it seems reasonable wherever possible to minimize surveys, interviews, and additional study visits.<sup>62</sup> These are all burdens that investigators routinely consider carefully in designing studies. However, there may be other needs and concerns that may be unique to, or more common in, patients near the end of life.

Although it is intuitively obvious that all research subjects would like to avoid the added time commitment and inconvenience of travel to and from additional appointment, this concern may be especially important to patients near the end of life, for whom long periods of time spent

sitting in a car can exacerbate discomfort. Similarly, patients may view surveys and questionnaires not only as time-consuming but also as drains on their energy. Therefore, investigators who conduct palliative care research may have an added reason to minimize the burdens of extra visits and data collection procedures, and to rely on telephone data collection strategies whenever possible.

Palliative care investigators may also need to consider the burdens that a study creates for friends and family members who often take on substantial burdens as caregivers.<sup>63</sup> Although most of the burdens of research participation are borne by the subject, the requirements of time, travel, and perhaps time off from work create burdens for others. By building flexibility into a study design (e.g., use of brief telephone interviews, multiple options for timing of clinic visits) investigators may be able to reduce the burdens of research participation on others.

#### *Risks and burdens: summary and recommendations*

The nature of the end-of-life study population creates significant challenges for investigators who attempt to minimize the risks and burdens that subjects will face. To assist investigators in conducting studies that minimize risks and burdens as much as possible, funders should:

- Support research that better defines the risks and burdens that are important to patients near the end of life and their families
- Encourage and support investigators’ efforts to minimize burdens through novel data collection techniques (e.g., automated telephone data collection)
- Support research to develop abbreviated forms of existing measurement instruments
- Encourage studies that provide all subjects with access to the standard of care.

## ENSURING DECISION-MAKING CAPACITY

Patients who consent to participate in research should have adequate decision-making capacity, which refers to subjects’ ability to understand relevant information, to appreciate the significance of that information, and to reason through to a



conclusion that makes sense for them.<sup>64</sup> These concerns are not unique, and parallel concerns in research involving patients with dementia<sup>65</sup> and psychiatric illness,<sup>66</sup> among others. However, deficits in decision-making capacity may create several additional challenges for palliative care investigators.

First, concern about capacity is particularly significant given the prevalence of cognitive impairment at the end of life.<sup>67–69</sup> Cognitive impairment occurs in 10–40% of patients in the final months and in up to 85% of patients in the last days of life.<sup>68,70</sup> Cognitive impairment may be difficult to identify in palliative care research because decision-making capacity varies over time,<sup>71</sup> and because impairment may result from the experimental or therapeutic medications themselves, such as opioids, benzodiazepines, or corticosteroids. Investigators who conduct trials of medications will encounter these challenges even more frequently if trials are designed to evaluate treatments for delirium, for which cognitive impairment is an inclusion criterion.<sup>72</sup>

Second, the effects of cognitive impairment on comprehension may be complicated by clinical depression, which occurs in between 5% and 25% of patients near the end of life.<sup>41</sup> Clinically significant adjustment disorders may be even more common.<sup>40</sup> It is possible that these disorders may impair either comprehension or decision making or both,<sup>73</sup> but studies designed to answer this issue have produced mixed results.<sup>66,74</sup>

Third, even in the absence of overt cognitive impairment or depression, it is possible that severe symptoms or affective disorders may impair subjects' ability to understand the risks and benefits of research participation. For some studies, particularly clinical trials, the presence of one or more of these intractable symptoms is an inclusion criterion.<sup>75</sup> It is possible that severe symptoms may impair comprehension if patients are unable to concentrate on the information offered in the informed consent process.<sup>76</sup> Although one study has failed to find an association between symptom burden and decision-making capacity, this relationship remains plausible and worthy of further study.<sup>74</sup>

Finally, these challenges may be compounded in prospective studies that require participation over days or weeks. In these studies, even if patients have the capacity to consent at the time of enrollment, they may not retain that capacity throughout the study. Thus days or weeks after patients give consent to participate, they may be

unable to understand changes in their condition clearly enough to withdraw. The result can be a "Ulysses contract" of sorts, in which research subjects find it easier to enroll than they do to withdraw.<sup>77</sup>

None of these challenges is easily remedied. Indeed, it is obstacles like these that lead some authors to argue that patients near the end of life should not be allowed to enroll in research.<sup>5</sup> Nevertheless, palliative care investigators have several concrete opportunities to enhance the ethical quality of palliative care research when decision-making capacity is uncertain.

First, at a minimum, investigators whose research involves patients near the end of life who are likely to lack decision-making capacity might institute brief assessments of understanding. Although this strategy cannot assess decision-making capacity, a few simple questions in either open-ended or multiple choice format provide a brief assessment of understanding.<sup>78</sup> In some situations, investigators may wish to assess decision-making capacity more formally using validated instruments such as the MacArthur Competency Assessment Tool for Research.<sup>66</sup>

These sorts of safeguards need not be employed in all studies. Instead, their use should be guided by the prevalence of cognitive impairment in a study population and by the balance of risks and benefits that a study offers.<sup>29,79</sup> For instance, when palliative care research involves only interviews or behavioral interventions that pose minimal risks, informal capacity assessments are generally sufficient. "Minimal risks" are defined as those risks that are encountered during a patient's usual care, or in everyday life.<sup>4</sup> When research poses greater than minimal risks, but offers potential benefits, some assessment of understanding may be appropriate. This research includes studies that involve a placebo or invasive interventions such as nerve blocks or epidural catheters. When a study that poses greater than minimal risks does not offer potential benefits, or is conducted in a population in which the prevalence of cognitive impairment is high (e.g., an inpatient hospice unit), a formal evaluation of capacity should be considered. This research includes studies that involve a placebo when an effective agent is available, and some pharmacokinetic/pharmacodynamic studies that require repeated blood samples and prolonged observation, without potential benefits.<sup>80</sup>

If a patient does not have the capacity to give consent, a legally authorized representative may

be able to give consent for research. This follows from federal guidelines governing research involving children,<sup>4</sup> and is justified by the argument that surrogate decision makers should be allowed to consent to research, just as they are allowed to consent to medical therapy. However, as with other research that involves patients without capacity to consent, investigators should be aware of applicable state laws that may restrict or even prohibit surrogate consent for research. If a patient does not have the capacity to consent, but is still able to participate in decisions, investigators should obtain assent from the patient and informed consent from the patient's surrogate.<sup>81</sup> This "dual consent" ensures that patients are as involved in the decision as possible, yet provides the additional protection of a surrogate's consent.

If a patient has decision-making capacity intermittently or is expected to lose capacity, investigators may obtain advance consent. This approach has been used in a study of treatment for delirium, in which informed consent was obtained from patients while they had decision-making capacity.<sup>72</sup> Advance consent should be obtained only for specific studies, and should be obtained close to the planned start of research, for instance, at the time of hospitalization or enrollment in a hospice or palliative care program.

#### *Decision-making capacity: summary and recommendations*

Investigators whose research involves patients near the end of life face considerable challenges of assessing and ensuring their subjects' decision-making capacity. To support investigators' efforts to enhance the quality of informed consent in this population, funders should:

- Support research to define the prevalence of impaired decision-making capacity and to identify predictors of impaired capacity
- Support the development of guidelines that specify the need for assessments of capacity
- Encourage and support investigators to include informed consent safeguards in study protocols where appropriate (e.g., capacity assessments, dual consent).

### PROTECTING VOLUNTARINESS

Another way that investigators can enhance the ethical soundness of a study's design is to en-

sure that subjects' participation is voluntary. In general terms, a choice is voluntary if it is made without significant controlling influences.<sup>82</sup> At first glance, assurances of voluntariness appear to be an issue of informed consent, and in fact for the most part they are. However, a study's design and plan for subject selection and recruitment may have as great an influence on subjects' freedom to refuse research participation as does the informed consent process. In particular, two features of a study's design are relevant. First, a prospective subject's choice must be made with full knowledge of available alternatives.<sup>4</sup> Second, the subject's choice must be made with the understanding that he or she can withdraw at any time.<sup>4</sup> Each of these creates opportunities in a study's design to ensure voluntariness that are discussed below.

#### *Reasonable alternatives to participation*

First, investigators can make sure that a study recruits subjects from an environment with excellent standards of palliative care. If patients generally receive excellent care, they will be best able to make a free and uncoerced choice about research participation. If, however, patients do not have access to a bare minimum of treatment options and expertise, they may view research participation more favorably, out of desperation.

One solution, albeit a somewhat draconian one, would be to require that palliative care research be conducted only in settings in which patients have access to a full range of services, treatment, and expertise. Although this requirement would reduce the potential for research participation out of desperation, it would effectively limit research to a small number of academic centers, with a possible loss of generalizability. Another more practical option might be to include a lead-in phase when clinical pain research is conducted in settings where the standard of care is poor. A lead in phase allows an opportunity to optimize palliative care before recruitment. This strategy not only has ethical value but scientific value as well because it provides a uniform baseline before randomization.

#### *Opportunities to withdraw*

Investigators can also enhance the ethics of a study's design by ensuring that subjects are able to withdraw at any time. Although a subject's ability to withdraw should be a fundamental aspect of any ethical research,<sup>4</sup> there may be unique

barriers to withdrawal from palliative care research. For instance, subjects who withdraw from clinical pain research that involves one or more medications will usually need access to a different medication upon withdrawal. This problem may be straightforward in many cases, but can be very challenging if in an interventional study if the investigational medication is an opioid, which requires the subject to get a new prescription and get it filled. Most states have created considerable barriers to opioid prescribing, including triplicate prescriptions, which may make it very difficult for a subject to obtain a new prescription and get it filled in a timely manner. If a subject has his or her medication available, the process may be easier. Nevertheless, considerable challenges of calculating an equianalgesic dose remain. For both of these reasons, investigators can enhance the ethical design of pain research by developing mechanisms to ensure that subjects who drop out continue to receive adequate pain treatment with as little interruption as possible.

#### *Voluntariness: summary and recommendations*

The nature of the end-of-life research population may make truly voluntary research participation difficult in some settings. To promote studies that improve voluntariness, funders should:

- Encourage studies at sites where all patients (both on and off protocol) will have access to high-quality palliative care
- Encourage investigators to develop effective mechanisms for subject withdrawal that ensure continuous access to care.

### CONCLUSION

The field of palliative care, and the standard of care that it represents, depend on rigorous research to provide data that will guide clinical care. Although this research raises substantial ethical questions, these questions need not curtail what promises to be a valuable, and highly productive area of research. Of course, the concerns discussed above should be taken seriously; to do otherwise risks the sorts of ethical missteps that have produced scandals in other fields. Nevertheless, these ethical questions can be addressed through careful planning and attention both to

the adequacy of a study's design and to the informed consent process.

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Address reprint requests to:  
 David Casarett, M.D., M.A.  
 University of Pennsylvania  
 3615 Chestnut Street  
 Philadelphia, PA 19104

E-mail: Casarett@mail.med.upenn.edu

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